8.0 EPIDEMIOLOGY OF THE LEUKEMIAS

STATEMENT TO THE PUBLIC

The reviewers expressed their judgments using two distinct sets of guidelines to evaluate the evidence:

- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for childhood leukemia, their classifications for EMFs ranged from "human carcinogen" to "probable human carcinogen" to "possible human carcinogen" (IARC's Groups 1, 2A, 2B). Panels convened by IARC and the National Institutes for Environmental Health Sciences classified EMFs as a "possible human carcinogen" for childhood leukemia.***
- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for adult leukemia, their classifications for EMFs ranged from "human carcinogen" to "possible human carcinogen" (IARC's Group 1 and 2B). The IARC Working Group classified the EMF evidence on adult leukemia as "inadequate." The National Institutes for Environmental Health Sciences classified it as "possible."***
- ***Using the Guidelines developed especially for the California EMF program, one of the reviewers "strongly believes" that high residential EMFs cause some degree of increased risk of childhood leukemia, another was "prone to believe" that they do, and another was "close to the dividing line between believing or not believing."***
- ***Using the Guidelines developed especially for the California EMF program, one of the reviewers was " prone to believe" that high residential or occupational EMFs cause some degree of increased risk of adult leukemia, while the other two were "close to the dividing line between believing or not believing."***

There are several reasons for the differences between the DHS reviewers and those of IARC. The three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them. Adult leukemia has an incidence of around 1/10,000 per year. If one doubled this rate to 2/10,000 per year and accumulated it over a lifetime of continuous high exposure one would accumulate a lifetime risk of 1%. Thus the vast majority (99%) of highly exposed people would still not contract this disease. Furthermore, calculations suggest that the fraction of all cases of childhood leukemia that one could attribute to EMFs would be no more than a few percent of the total cases (if any). Similar considerations apply to adult leukemia. Nevertheless, if EMFs do contribute to the cause of this condition, even the low fractions of attributable cases and the size of accumulated lifetime risk of highly exposed individuals could be of concern to regulators. Indeed, when deemed a real cause, estimated lifetime risks smaller than this (1/100,000) have triggered regulatory evaluation and, sometimes, actual regulation of chemical agents such as airborne benzene. The uncommon, accumulated high-EMF exposures implicated by the evidence about these conditions come from unusual configurations of wiring in walls, grounded plumbing, nearby power lines, and exposure from some jobs in electrical occupations. There are ways to avoid these uncommon accumulated exposures by maintaining a distance from some appliances, changes in home wiring and plumbing, and power lines. However, to put things in perspective, individual decisions about things like buying a house or choosing a jogging route should involve the consideration of well-recognized certain risks, such as those from traffic, fire, flood, and crime, as well as the uncertain comparable risks from EMFs. The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the added personal risk suggested by the epidemiological studies was "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. The three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	RL*	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASE DISEASE RISK TO SOME DEGREE
Childhood Leukemia					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Strongly believe	140	
	2	2B	Close to dividing line	22	
	3	2A	Prone to believe	17	
Adult Leukemia					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Prone to believe	29	
	2	2B	Close to dividing Line	21	
	3	2B	Close to dividing Line	6	

8.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

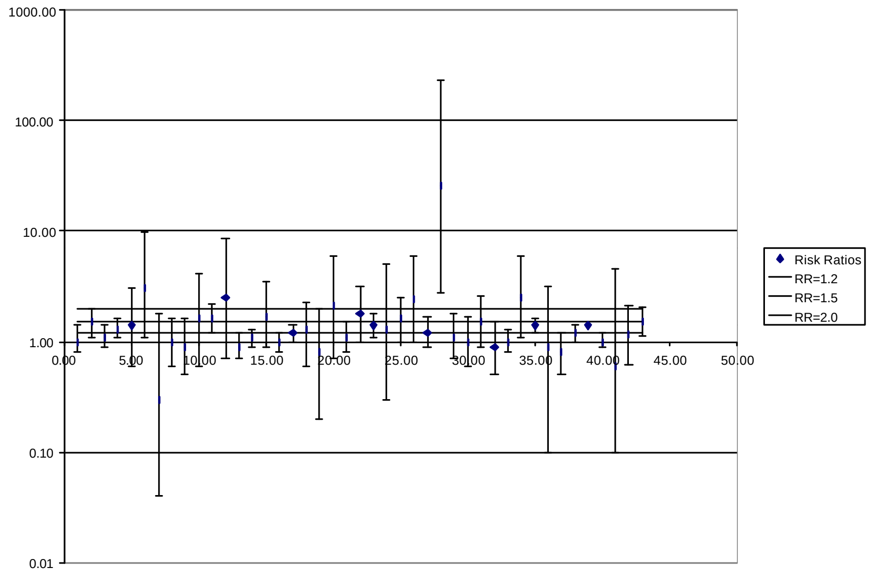


Figure 8.1.1 Studies of Adult Leukemia and EMFs Primarily Based on Kheifets (1997)

NOTE ON THE RISK ESTIMATES IN FIGURE 8.1.1 AND TABLE 8.1.1: Several studies report multiple comparisons (e.g., wire code classification or measured fields; dichotomous or polytomous classification; high vs. low or very high vs. very low). These different classifications lead to different risk estimates, and in a few cases the same data may show a positive association, no association or even a negative association depending on the method of analysis. For the sign test, widely employed in this evaluation, it is important that one and only one result be included from each study. In all cases, the DHS reviewers refrained from making the selection themselves to avoid introducing a subjective bias. Whenever the studies hade been included in a meta-analysis or pooled analysis, they accepted the selection made by the analysts. If a study had not been included in a meta-analysis or pooled analysis, but such an analysis had been performed on other studies for the same endpoint, the reviewers used the same guidelines used in those analyses. For example, the UK study (2000) shows a positive association for a 4 mG cutpoint, but the reviewers report it as negative because most of the other childhood leukemia studies were included in a pooled analysis (Greenland et al., 2000) in which the comparison was made for exposure above 3 mG vs. an exposure < 1 mG and using these cutpoints on the UK data yields a negative association. When no meta-analyses exist, the reviewers used the RR chosen by the authors to summarize their findings, usually in the abstract. These considerations apply to all similar tables/figures in the following chapters.

Figure 8.1.1 and Table 8.1.1 summarize the epidemiological evidence for adult leukemia derived primarily from (Kheifets et al., 1997a) of 43 studies, 29 had odds ratios (ORs) above 1.00 ($p=\leq 0.01$), 20 had ORs above 1.2. The meta-analytic summary was 1.2.

Figure 8.1.2 and Table 8.1.2 summarize the childhood leukemia epidemiological literature. Sixteen of nineteen had ORs > 1.00 ($p = 0.0004$), fifteen of nineteen were above 1.2, nineteen had ORs > 1.5. A meta-analysis by (Wartenberg, 2001) suggests a meta-analytic summary OR of 1.3 (1.0-1.7). Greenland et al. (Greenland et al., 2000) presents the information in Table 8.1.3 with a pooled analysis OR conveyed by being above 3 mG of 1.69 (1.25, 2.29).

TABLE 8.1.1 SUMMARY OF ADULT LEUKEMIA STUDIES

Study	Study No.	Year	Individual Odds Ratio Mean	Lower CL	Upper CL	Source
Savitz & Loomis	1.00	1995	1.00	0.80	1.40	Kheifets 1997
Floderus et al.	2.00	1992	1.50	1.10	2.00	Kheifets 1997
Floderus et al.	3.00	1994	1.10	0.90	1.40	Kheifets 1997
London et al.	4.00	1994	1.30	1.10	1.60	Kheifets 1997
Thierault et al.	5.00	1994	1.40	0.60	3.10	Kheifets 1997
Thierault et al.	6.00	1994	3.10	1.10	9.70	Kheifets 1997
Thierault et al.	7.00	1994	0.30	0.04	1.80	Kheifets 1997
Tynes et al.	8.00	1994	1.00	0.60	1.60	Kheifets 1997
Tynes et al.	9.00	1994	0.90	0.50	1.60	Kheifets 1997
Ciccone et al.	10.00	1993	1.60	0.60	4.10	Kheifets 1997
Guenel et al.	11.00	1993	1.60	1.20	2.20	Kheifets 1997
Matanowski et al.	12.00	1993	2.50	0.70	8.60	Kheifets 1997
Sahl et al.	13.00	1993	0.90	0.70	1.20	Kheifets 1997
Tynes et al.	14.00	1992	1.10	0.90	1.30	Kheifets 1997
Richardson et al.	15.00	1992	1.70	0.90	3.50	Kheifets 1997
Loomis et al.	16.00	1991	1.00	0.80	1.20	Kheifets 1997
Robinson et al.	17.00	1991	1.20	1.00	1.40	Kheifets 1997
Simonato	18.00	1991	1.30	0.60	2.30	Kheifets 1997
Spinelli et al.	19.00	1991	0.80	0.20	2.00	Kheifets 1997
Flodin et al.	20.00	1990	2.10	0.70	5.90	Kheifets 1997
Gallagher et al.	21.00	1990	1.10	0.80	1.50	Kheifets 1997
Garland et al .	22.00	1990	1.80	1.00	3.20	Kheifets 1997
Juutilainen et al.	23.00	1990	1.40	1.10	1.80	Kheifets 1997
Guberan et al.	24.00	1989	1.30	0.30	5.00	Kheifets 1997
Pearce et al.	25.00	1989	1.60	1.00	2.50	Kheifets 1997
Cartwright et al.	26.00	1988	2.40	1.00	6.00	Kheifets 1997
Milham et al.	27.00	1988	1.20	0.90	1.70	Kheifets 1997
Preston-Martin et al.	28.00	1988	25.40	2.80	232.50	Kheifets 1997
Tola et al.	29.00	1988	1.10	0.70	1.80	Kheifets 1997
Olsen et al.	30.00	1987	1.00	0.60	1.70	Kheifets 1997
Stern et al.	31.00	1986	1.50	0.90	2.60	Kheifets 1997
Blair et al.	32.00	1985	0.90	0.50	1.50	Kheifets 1997
Calle et al.	33.00	1985	1.00	0.80	1.30	Kheifets 1997
Gillman et al.	34.00	1985	2.50	1.10	5.90	Kheifets 1997
Milham et al.	35.00	1985	1.40	1.20	1.60	Kheifets 1997
Olin et al.	36.00	1985	0.90	0.10	3.20	Kheifets 1997
Morton et al.	37.00	1984	0.80	0.50	1.20	Kheifets 1997
Coleman et al.	38.00	1983	1.20	1.00	1.40	Kheifets 1997
Howe et al.	39.00	1983	1.40			Kheifets 1997
McDowall et al.	40.00	1983	1.00	0.90	1.20	Kheifets 1997
Polednak	41.00	1981	0.60	0.10	4.50	Kheifets 1997
Severson	42.00	1988	1.15	0.62	2.15	Severson 1988
Wertheimer & Leeper	43.00	1982	1.51	1.11	2.05	Wertheimer & L. 1982

Note: CL = confidence Limit

Fig 8.1.2 Summary Graphic Representation of the Results of Childhood Leukemia Studies

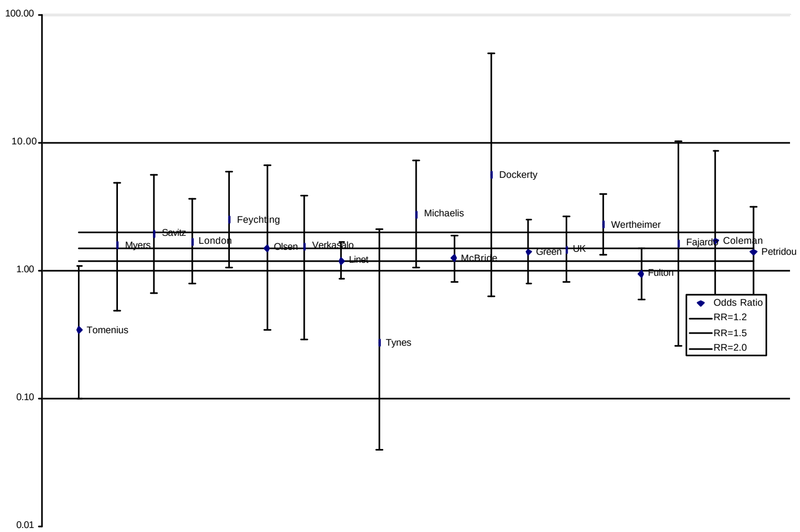


TABLE 8.1.2

From Wartenberg, Childhood Leukemia

Author	Exposure Definition	Study No.	Individual Odds Ratio, Mean	Lower CL	Upper CL
Tomenius	0.3 µT spot	1	0.34	0.10	1.09
Myers	0.03 µT peak	2	1.56	0.49	4.91
Savitz	0.2 µT spot	3	1.93	0.67	5.56
London	0.27 µT 24-hour	4	1.68	0.78	3.64
Feychting	0.2 µT calculated	5	2.49	1.04	5.98
Olsen	0.25 µT calculated	6	1.50	0.34	6.73
Verkasalo+	0.20 µT calculated	7	1.55	0.29	3.81
Linet	0.2 µT 24-hour	8	1.19	0.85	1.68
Tynes	0.14 µT calculated TWA	9	0.27	0.04	2.10
Michaelis	0.2 µT 24-hour	10	2.74	1.04	7.21
McBride	0.2 µT spot	11	1.25	0.82	1.89
Dockerty	0.2 µT spot bedroom	12	5.57	0.62	50.03
Green	0.15 µT interior average	13	1.39	0.78	2.48
UK	0.2 µT calculated	14	1.46	0.81	2.64
Wertheimer	wire code	15	2.28	1.34	3.91
Fulton	wire code	16	0.95	0.60	1.50
Fajardo	wire code	17	1.64	0.26	10.29
Coleman	wire code	18	1.70	0.34	8.64
Petridou	wire code	19	1.39	0.61	3.18

Note: CL = confidence Limit

TABLE 8.1.3 SUMMARY DESCRIPTION OF ADULT LEUKEMIA STUDIES

INVESTIGATOR AND DATE (REFERENCE NUMBER)	STUDY POPULATION AND LOCATION	METHOD USED FOR EXPOSURE ESTIMATE	STUDY TYPE	NUMBER OF CASES OR STUDY SUBJECTS	RISK MEASURE	ALL LEUK.	AML	ALL	CLL	CML
(Savitz & Loomis, 1995)	US: deaths among 138,905 men employed full-time at least 6 months, 1950-1986, at 5 utility companies (all members of the EPRI)	Work history and measurements	cohort	164 cases of leukemia	RR	1.0 (0.8-1.4)	0.9 (0.5-1.6)			1.0 (0.5-2.0)
(Floderus, 1993) (Floderus, 1992)	Sweden: cases among males in 1980 employed and living in mid-Sweden, 1983-1987	Usual job and measurements	CC	250 cases of leukemia; age 20-64	OR	1.5 (1.1-2.0)	0.9 (0.6-1.4)		2.5 (1.6-3.9)	
(Floderus et al., 1994) (Tornqvist et al., 1991) Linet et al. 1988 (7) (Tornqvist, Norell & Knave, 1986)	Sweden: 1,906,660 men employed in 1960, followed from 1961-1979 (133,687 in selected electrical occupations)	Occupation code from census (with estimation of EMF exposure)	cohort	334 cases of leukemia (in selected electrical occupations); age 20-74	SMR	1.1 (0.9-1.4)	1.1 (0.8-1.6)	1.3 (0.4-4.2)	1.2 (0.8-1.8)	1.1 (0.6-1.6)
(London et al., 1994) (Wright, Peters & Mack, 1982)	US: cases among males with known occupation, in Los Angeles County Cancer Registry & measurements, 1972-1990	Occupation code from Registry	MOR	2,355 cases of leukemia; age 20-64	OR	1.3 (1.1-1.6)			1.3 (1.0-1.8)	1.3 (0.8-2.1)
(Theriault et al., 1994)	France: cases among 170,000 active male utility workers at Electricité de France-Gas de France from 1978-1989	Work history and measurements	CC	71 cases of leukemia	OR	1.4 (0.6-3.1)	1.7 (0.5-5.5)		4.8 (0.5-70.6)	
(Theriault et al., 1994)	Canada: cases among 31,543 men employed at Ontario Hydro on Jan. 1, 1973 and new employees, 1973-1988	Work history and measurements	CC	45 cases of leukemia	OR	3.1 (1.1-9.7)	37.8 (3.5->100)		2.1 (0.4-11.6)	

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Theriault et al., 1994)	Canada: cases among 21,749 men employed at Hydro-Quebec on Jan. 1, 1970 and new employees, 1970-1988	Work history and measurements	CC	24 cases of leukemia	OR	0.3 (0.04-1.8)			0.3 (0.02-2.6)	
(Tynes et al., 1994a)	Norway: cases among 13,030 male Norwegian railway workers, 1958-1990	Work history and measurements	CC	52 cases of leukemia	OR	1.0 (0.6-1.6)				
(Tynes et al., 1994b)	Norway: cases of cancer among cohort of 5,088 male workers in 8 large Norwegian hydroelectric power companies, employed at least 1 yr, 1953-1991	Work history and measurements	cohort	11 cases of leukemia	SIR	0.9 (0.5-1.6)				
(Ciccone et al., 1993)	Italy: cases of acute or chronic myeloid leukemia or MDS in main hospital, Torino, Italy, Oct. 1989-1990	Work history (assessed probability of exposure to EMF)	CC	50 cases of AML 17 cases of CML 19 cases of MDS; age 15-74	OR	AML+ CML+ MDS: Males: 1.6 (0.6-4.1)				
(Guenel et al., 1993)	Denmark: cases among 2.8 million Danes, 1970-1987	Occupation code from Central Population Register and measurements	cohort	39 male cases of leukemia; age 20-64	SIR	1.6 (1.2-2.2)	1.4 (0.9-2.4) All acute			
(Matanoski et al., 1993) (19)	US: cases among white males employed at least 2 years, identified from mortality records of ATT, 1975-1980	Work history and measurements	CC	124 cases of leukemia	OR	2.5 (0.7-8.6)				

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Sahl et al., 1993)	US: deaths among 36,221 employees at Southern California Edison Company, 1960-1988	Work history and measurements	CC and cohort	44 cases of leukemia	OR	0.9 (0.7-1.2)				
(Tynes, Andersen & Langmark, 1992)	Norway: cases among cohort of 37,945 male Norwegian electrical workers, 1961-1985	Job titles from census (categorized into 5 levels of exposure)	cohort	107 cases of leukemia	SIR	1.1 (0-9-1.3)	1.3 (0.9-1.2)	1.4 (0.4-3.7)	1.0 (0.6-1.4)	1.5 (0.9-2.3)
(Richardson, 1992) (Bastuji-Garin, 1990)	France: cases in 2 hospitals, 1984-1988	Work history and measurements	CC	185 cases of leukemia (50.2% cases male); age 30	OR	1.7 (0.9-3.5)	4.8 (1.5-15.8) All acute			
(Loomis, 1991) (Loomis & Savitz, 1990)	US: cases among 410,651 male deaths in 16 US states, 1985-1986	Occupation code from death certificates	MOR	3,400 cases of leukemia; age 20	OR	1.0 (0.8-1.2)	1.1 (0.7-1.7)	1.5 (0.7-3.4)	0.6 (0.3-1.1)	
(Robinson et al., 1991)	US: deaths identified from industrial mortality data, 14 states, 1979-1985	Occupation code from mortality data	PMR	183 cases of leukemia	PMR	1.2 (1.0-1.4)	1.1 (0.9-1.5)			
(Simonato et al., 1991)	Europe: cases of cancer among a cohort of 11,902 male welders from 135 companies located in 9 European countries	Work history and type of welding, if known	cohort	11 cases of leukemia	SIR	1.3 (0.6-2.3)				
(Spinelli, 1991)	British Colombia: cases of cancer, 1970-1985; deaths from cancer, 1950-1985; among male workers with 5 or more yrs of experience in an aluminum induction plant	Industrial hygienist identified EMF exposure for each job in company records	cohort	7 cases of leukemia total (mortality data) 3 incident cases of leukemia	SIR	0.8 (0.2-2.0)				
(Flodin, 1990) (Flodin, Fredriksson & Axelson, 1986)	Sweden: cases of AML from hospitals in 4 countries, 1977-1985	Occupation from postal questionnaire	CC	86 cases of AML; age 20-70	OR		2.1 (0.7-5.9)			

INVESTIGATOR AND DATE (REFERENCE NUMBER)	STUDY POPULATION AND LOCATION	METHOD USED FOR EXPOSURE ESTIMATE	STUDY TYPE	NUMBER OF CASES OR STUDY SUBJECTS	RISK MEASURE	ALL LEUK.	AML	ALL	CLL	CML
(Gallagher et al., 1990)	Canada: deaths among males in British Colombia, 1950-1984	Occupation code	PMR	35 cases of leukemia; age 20-65	PMR	1.1 (0.8-1.5)				
(Garland, 1990)	US: cases of cancer among white, male active-duty, enlisted naval personnel, 1974-1984	Work history	cohort	102 cases of leukemia; age 17-64	SIR	1.8 (1.0-3.2)				
(Juutilainen, Laara & Pukkala, 1990) (Juutilainen, 1988)	Finland: cases among all male industrial workers, 1971-1980	Occupation code from census (categorized as probable, possible, or no exposure to ELF)	cohort	221 cases of leukemia	RR	1.4	1.4			
(Guberan, 1989)	Switzerland: cases among 1,916 male painters and 1,948 male electricians in Geneva, 1970-1984	Occupation code from census	cohort	2 cases of leukemia	SIR	1.3 (0.3-5.0)				
(Pearce, Reif & Fraser, 1989) (Pearce et al., 1986) (22) (Pearce et al., 1985)	New Zealand: cases among males from New Zealand Cancer Registry, 1979-1983	Occupation code from Registry	MOR	546 cases of leukemia; age ≥ 20	OR	1.6 (1.0-2.5)	1.2 (0.4-3.9)		3.4 (1.38-8.9)	0.9 (0.1-6.4)
(Cartwright, 1988)	Yorkshire, UK: cases of AML in hospitals throughout Yorkshire, excluding South Humberside, 1979-1986	Work history from interview	CC	161 cases of leukemia; age ≥ 15	RR		2.4 (1.0-6.0)			
(Milham, 1988) (Milham, 1985)	US: deaths among 67,829 male licensed amateur radio operators in Washington State and California, 1979-1984	Amateur radio operator license, according to FCC files	cohort	36 cases of leukemia	SMR	1.2 (0.9-1.7)	1.8 (1.0-2.9)	1.2 (0.3-3.8)	1.1 (0.4-2.4)	0.9 (0.2-2.5)

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Preston-Martin & Peters, 1988)	US: cases of CML from the Los Angeles County Cancer Registry, April 1, 1979-June 30, 1985	Ever employed in one of 11 specific job titles from questionnaire data	CC	137 CML cases; age 20-69	OR					25.4 (2.8-232.5)
(Tola et al., 1988)	Finland: cases of cancer in Finnish Cancer Registry among cohort of 12,693 male shipyard and machine shop workers, 1945-1960	Work history	cohort	19 cases of leukemia	SIR	All workers: 1.1 (0.7-1.8) welders: 0.9 (0.1-3.3)				
(Olsen, 1987)	Denmark: 93,810 cases (male and female) from Danish Cancer Registry, 1970-1979	Work history	PIR	1,402 cases of acute leukemia	SPIR	1.0 (0.6-1.7)				
(Stern et al., 1986)	US: deaths among 24,545 onshore workers at Portsmouth Naval Shipyard, 1952-Aug 1977	Work history	CC	53 cases of leukemia	OR	1.5 (0.9-2.6)				
(Blair, 1985)	US: 107,563 deaths analyzed among cohort of 293,958 veterans, 1954-1970	Usual occupation from questionnaires	cohort	cases of leukemia; age 31-84	SMR	0.9 (0.5-1.5)				
(Calle & Savitz, 1985)	US: deaths among white men in Wisconsin for 10 electrical occupations, 1963-1978	Occupation code from mortality data (used occupational groups based on Milham data)	PMR	81 cases of leukemia 41 cases of acute leukemia; age ≥ 20	PMR	1.0 (0.8-1.3)	1.1 (41 cases) All acute			

INVESTIGATOR AND DATE (REFERENCE NUMBER)	STUDY POPULATION AND LOCATION	METHOD USED FOR EXPOSURE ESTIMATE	STUDY TYPE	NUMBER OF CASES OR STUDY SUBJECTS	RISK MEASURE	ALL LEUK.	AML	ALL	CLL	CML
(Gilman, 1985)	US: 19,000 male coal miners entered into 4 NIOSH cohorts; 6,066 death certificates reviewed, prior to 1985	No. of years of underground mining, employment at time of cohort creation	MOR	40 cases of leukemia	OR	2.5 (1.1-5.9)	3.8	0.6	6.3 (*P* < 0.05)	
(Milham, 1985b) (Milham, 1982)	US: deaths among 486,000 total deaths in white males in Washington state, 1950-1982	Occupation code from mortality data	PMR	146 cases of leukemia 67 cases of acute leukemia; age ≥ 20	PMR	1.4 (1.2-1.6)	1.6 (67 cases) All acute			
(Olin, Vagero & Ahlbom, 1985)	Sweden: deaths among 1,245 male electrical engineers from Royal Institute of Technology in Stockholm, 1930-1979	MS in electrical engineering from Royal Institute of Technology, 1930-1959	cohort	2 cases of leukemia	SMR	0.9 (0.1-3.2)				
(Morton, 1984)	US: cases among total resident population of 4 counties of Portland/ Vancouver, 1963-1977	Usual occupation for cases, occupation code only for non-cases	cohort	1,678 cases of leukemia; age ≥ 16	SMR	0.8 (0.5-1.2)				
(Coleman, Bell & Skeet, 1983)	England: cases among 6.5 million identified through South Thames Cancer Registry, 1961-1979	Occupation code from Registry	PIR	113 cases of leukemia; age 15-74	PIR	1.2 (1.0-1.4)	1.2 (33 cases)	1.5 (12 cases)	1.3 (33 cases)	0.9 (6 cases)
(Howe, 1983)	Canada: deaths among 415,201 males In Canadian labor force, 1965-1971	Occupation code from census and work history	cohort	154 deaths from leukemia and leukemia; 31 cases among transportation communication, and other utility workers	SMR	1.4 (31 cases)				
(McDowall, 1983)	England and Wales: deaths among males, 1970-1972	Occupation code from mortality data	PMR	85 cases of leukemia 11 cases of ALL 31 cases of AML; age 15-74	PMR	1.0 (0-9-1.2)	1.0 (31 cases)	1.0 (1 case)		

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(McDowall, 1983)	England & Wales: deaths among males, 1970-1972	Occupation code from mortality data	MOR	537 AML cases; age ≥ 15	RR		2.1	(1.3-3.6)		
(Polednak, 1981)	US: deaths among 1,059 while male welders at 3 plants in Oak Ridge, Tennessee, employed 1943-1973	Work history	cohort	1 case of leukemia	SMR	0.6 (0.1-4.5)				
(Severson et al., 1988)	Residents of Seattle, Washington	Wire coding	Case control	114	OR		1.15 (0.62-2.15)			
(Wertheimer & Leeper, 1982)	Residents of Denver, Colorado, and neighboring towns	Wire coding	Case control	1179	OR	1.51 (1.11-2.05)				

TABLE 8.1.4 SUMMARY DESCRIPTION OF CHILDHOOD LEUKEMIA STUDIES

STUDIES WIRE CODES	EXPOSURE CLASSIFICATI ON	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
(Wertheimer & Leeper, 1979)	Birth address: LCC HCC Death address: LCC HCC	84 52 92 63	Reference 2.28 (1.34-3.91) Reference 2.98 (1.78-4.98)		
(Savitz et al., 1988)	HCC/LCC VHCC/Buried	27/70 7/28	1.54 (0.90-2.63) 2.75 (0.94-8.04)	<19/59 6/24	1.28 (0.70-2.34) 2.75 (0.90-8.44)
(London et al., 1991)	UG+VL OLCC OHCC VHCC	31 58 80 42	References 0.95 (0.53-1.69) 1.44 (0.81-2.56) 2.15 (1.08-4.26)		
(Linet et al., 1997)	UG+VLCC OLCC OHCC VHCC			175 116 87 24	Rreferences 1.07 (0.74-1.54) 0.99 (0.67-1.48) 0.88 (0.48-1.63)
(McBride et al., 1999)	VHCC+OHCC	351	0.97 (0.72-1.32)		
CALCULATED FIELDS					
(Feychting & Ahlbom, 1993)	Unmatched analyses (FμT) <0.10.1-0.19 >0.2 >0.3 Matched analyses: (FμT) 0.1-0.19 >0.2	274 7 7	References 2.1 (0.6-6.1) 2.7 (1.0-6.3) 3.8 (1.4-9.3) 4.3 (1.0-8.9) 3.5 (0.9-13.6)		

STUDIES WIRE CODES	**EXPOSURE CLASSIFICATION**	**LEUKEMIA NO. CASES**	**RR (95% CI)**	**ACUTE LYMPHOBLASTIC NO. OF CASES**	**RR (95% CI)**
(Olsen, Nielsen & Schulgen, 1993)	(µT) < 0.1 0.1-0.24 ≥0.25 ≥0.40	 829 1 3 3	 References 0.5 (0.1-4.3) 1.5 (0.3-6.7) 6.0 (0.8-44)		
(Verkasalo et al., 1993), (Verkasalo et al., 1994)	Cumulative exposure (µT-years) 0.01-0.39 ≥0.40 ≥1.0 Average exposure (µT) 0.01-0.19 ≥0.2	32 3 3 32 3	0.90 (0.62-1.3) 1.2 (0.26-3.6) 3.5 (0.7-10) 0.89 (0.61-1.3) 1.6 (0.32-4.5)		
(Tynes & Haldorsen, 1997)	Average exposure (µT) < 0.05 0.05-0.13 ≥0.14 Closest to diagnosis (µT) <0.05 0.05-0.13 ≥0.14 ≥0.2	 139 8 1 134 10 4 2	 References 1.8 (0.7-4.2) 0.3 (0.0-2.1) References 1.5 (0.7-3.3) 0.8 (0.3-2.4) 0.5 (0.1-2.2)		
PROXIMITY TO SOURCES					
(Coleman et al., 1989)	< 25 m substation ≥ 25 m substation	81 3	Reference 1.7(0.31-8.64)		
(Myers et al., 1990)	< 25 m ≥25 m	173 7	Reference 1.56 (0.54-4.53)		
Fajardo 1992	< 20 m distribution ≥ 20 m distribution	43 3	Reference 1.64(0.26-10.29)		
(Petridou et al., 1993)	Categories 1-3 Categories 4,5	106 11	Reference 1.39 (0.61-3.18)		

STUDIES WIRE CODES	EXPOSURE CLASSIFICATION	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
HOME OR PERSONAL MEASUREMENTS					
(Tomenius, 1986)	<0.3μT ≥0.3μT	239 4	Reference 0.34 (0.10-1.09)		
(Myers et al., 1990)	<0.03μT peak ≥ 0.03μT peak	174 6	Reference 1.56 (0.49-4.91)		
(Savitz et al., 1988)	Low power conditions (μT) < 0.2 ≥0.2 High power conditions (μT) < 0.2 ≥0.2 Electric fields (μT) < 12 V/m ≥12 V/m	 31 5 30 7 31 6	 Reference 1.93 (0.67-5.56) Reference 1.41 (0.57-3.50) Reference 0.75 (0.29-1.91)	 23 3 23 4 23 4	 Reference 1.56 (0.42-5.75) Reference 1.05 (0.34-3.26) Reference 0.67 (0.22-2.04)
(London, 1991)	Low power conditions (μT) < 0.032 0.032-0.067 0.068-0.124 ≥0.125	 67 34 23 16	 Reference 1.01 (0.61-1.69) 1.37 (0.65-2.91) 1.22 (0.52-2.82)		
(Michaelis et al., 1997a)	Short-term measurement (μT) < 0.2 ≥0.2	 170 6	 Reference 0.7 (0.3-1.8)		
(London, 1991)	24 hour measurements (μT) 0-0.067 0.068-0.118 0.119-0.267 ≥0 .268	 85 35 24 20	 Reference 0.68 (0.39-1.17) 0.89 (0.46-1.71) 1.48 (0.66-3.29)		

Studies wire codes	**Exposure classification**	**Leukemia no. cases**	**RR (95% CI)**	**Acute lymphoblastic no. of cases**	**RR (95% CI)**
(Michaelis et al., 1997a)	Median of measurements (µT)				
	< 0.2	125	Reference		
	≥0.2	4	3.2 (0.7-14.9)		
	Mean of measurements (µT)				
	< 0.2	125	Reference		
	≥0.2	4	1.5 (0.4-5.5)		
	Median during the night (µT)				
	< 0.2	1245	reference		
	≥0.2		3.9 (0.9-16.9)		
(Michaelis et al., 1997b)	Median of measurements				
	(FµT)	167	Reference		
	< 0.2	9	2.3 (0.8-6.7)		
	≥0.2				
	Median during the night (µT)	167	Reference		
	< 0.2	9	3.8 (1.2-11.9)		
	≥0.2				
(Linet et al., 1997)	Unmatch analysis (µT)				
	< 0.065			267	Reference
	0.065-0.099			123	1.1 (0.81-1.50)
	0.1-0.199			151	1.1 (0.83-1.48)
	0.2-0.299			38	0.92 (0.57-1.48)
	0.3-0.399			22	1.39 (0.72-2.72)
	0.4-0.499			14	3.28 (1.15-9.39)
	≥0.5			9	1.41 (0.49-4.09)
	≥0.2			83	1.24 (0.86-1.79)
	≥0.3			45	1.7 (1.0-2.9)
	Matched analysis (µT)				
	<0.065			206	Reference
	0.065-0.099			92	0.96 (0.65-1.40)
	0.1-0.199			107	1.15 (0.79-1.65)
	0.2-0.299			29	1.31 (0.68-2.51)
	0.3-0.399			14	1.46 (0.61-3.50)
	0.4-0.499			10	6.41 (1.30-31.73)
	≥0.5			5	1.01 (0.26-3.99)
	≥0.2			58	1.53 (0.91-2.56)

STUDIES WIRE CODES	EXPOSURE CLASSIFICATI ON	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
(UKCSS, 1999)	> 2 mG	1073	0.9 (0.49-1.63)	906	0.92 (0.47-1.79)
(Green et al., 1999a)	>1.5 mG (average indoor)	201	1.74 (0.63-4.82)	75	2.86 (0.88-9.29)
(Green et al., 1999b)	> 1.4 (personal exposure)	88	4.5 (1.3-1.9)	76	3.5 (0.9-13.9)
(McBride et al., 1999)	> 2 mG	297	1.35 (0.86-2.11)		

TABLE 8.1.5. STUDY-SPECIFIC ODDS-RATIO ESTIMATES AND STUDY-ADJUSTED SUMMARY ESTIMATES, MAGNETIC-FIELD DATA. REFERENCE CATEGORY: 0.1, µT.

(From "A POOLED ANALYSIS OF MAGNETIC FIELDS, WIRE CODES, AND CHILDHOOD LEUKEMIA," S. Greenland1, A. R. Sheppard2, W. T. Kaune3, C. Poole4, M.A. Kelsh5, for the Childhood Leukemia-EMF Study Group*)

First	Magnetic-field category (µT)		
Author	>0.1, 0.2	>0.2, 0.3	>0.3
Coghill	0.54 (0.17, 1.74)	no controls	no controls
Dockerty	0.65 (0.26, 1.63)	2.83 (0.29, 27.9)	no controls
Feychting	0.63 (0.08, 4.77)	0.90 (0.12, 7.00)	4.44 (1.67,11.7)
Linet	1.07 (0.82, 1.39)	1.01 (0.64, 1.59)	1.51 (0.92, 2.49)
London	0.96 (0.54, 1.73)	0.75 (0.22, 2.53)	1.53 (0.67, 3.50)
McBride	0.89 (0.62, 1.29)	1.27 (0.74, 2.20)	1.42 (0.63, 3.21)
Michaelis	1.45 (0.78, 2.72)	1.06 (0.27, 4.16)	2.48 (0.79, 7.81)
Olsen	0.67 (0.07, 6.42)	no cases	2.00 (0.40, 9.93)
Savitz	1.61 (0.64, 4.11)	1.29 (0.27, 6.26)	3.87 (0.87,17.3)
Tomenius	0.57 (0.33, 0.99)	0.88 (0.33, 2.36)	1.41 (0.38, 5.29)
Tynes	1.06 (0.25, 4.53)	no cases	no cases
Verkasalo	1.11 (0.14, 9.07)	no cases	2.00 (0.23,17.7)
Study-adjusted summaries:*			
Woolf	0.96 (0.81, 1.14)	1.08 (0.80, 1.45)	1.83 (1.34, 2.49)
MH	0.95 (0.80, 1.12)	1.06 (0.79, 1.42)	1.69 (1.25, 2.29)
Study + age + sex adjusted:†			
MH	1.01 (0.84, 1.21)	1.06 (0.78, 1.44)	1.68 (1.23, 2.31)
Spline‡	1.00 (0.81, 1.22)	1.13 (0.92, 1.39)	1.65 (1.15, 2.36)

*MH = Mantel-Haenszel; maximum-likelihood summaries differed by less than 1% from these summaries. Based on 2,656 cases and 7,084 controls. Summary tests: 3 df MH categorical P = 0.01; 1 df Mantel trend P = 0.06 (from continuous data).

†Excludes Tomenius (no covariate data). Based on 2,484 cases and 6,335 controls with age and sex data. 3 df MH categorical P = 0.01; 1 df Mantel trend P = 0.04 (from continuous data).

‡Estimates comparing odds at category means (0.14, 0.25, 0.58 versus 0.02 µT) from a quadratic logistic spline with one knot at 0.2 µT, plus age and sex terms.

8.2 Pro and Con Arguments for Childhood and Adult Leukemia

Table 8.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Results are due to chance and multiple comparisons.	(F1) Meta-analyses show that overall the association is statistically significant (e.g., unlikely to be due to chance).	(C1) The test of statistical significance on the pooled or meta-analyzed data show that chance is a very unikely explanation ($p<0.02$, one-sided).

TABLE 8.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Bias in some or all studies has been identified. Given the small size of the association and the inconsistencies between and within studies, bias is a plausible explanation for the positive results.	(F1) No bias candidate common to all studies. No evidence or argument for consistent, upward bias. On the contrary, there is evidence that bias has inconsistent direction.	(C1) Pooled analysis shows that most studies are very consistent. While consistency may be due to a common bias, the different environments, methods of subjects recruitments, and exposure assessment and study design make it unlikely that most studies were affected by the same bias.
(A2) In particular, the meta-analytical risk estimate for adult leukemia is VERY close to 1, very susceptible to bias.	(F2) Savitz control and specular control matrix (Zaffanella et al., 1998) exhibits asymmetry of opposite direction to asymmetry in London's control and specular control matrix, suggesting that control selection bias in the two cases were in opposite direction and that therefore they could not both have resulted in a upward bias of the risk estimate.	(C2) The only bias certainly common to all these studies is that deriving from non-differential exposure misclassification, which, in dichotomous analyses, tends to understimate effects in these studies and distorts dose response assessments.
(A3) Exposure assessment in Wertheimer and Leeper studies not blind.	(F3) Convincing evidence against publication bias for children in Wartenberg's meta-analysis (Wartenberg, 2001).	(C3) There is no evidence that bias resulting in an inflation of the risk estimates is common to all studies. The argument that so many positive risk estimates greater than unity are due to bias, although studies are different in design and population base is not convincing and does not diminish the credibility of the hypothesis much.
(A4) Some evidence of non-publication bias in adult studies (Kheifets, 2001).	(F4) Publication bias in adults, insufficient to explain association (Kheifets, 2001).	
(A5) Occupational studies of mixed quality.	(F5) Strong pressures to publish good negative studies.	
(A6) Different control series in Li and Theriault residential study yield different risk estimates.	(F6) In the comparative analyses (Kheifets et al., 1999) the pooled OR = 1.48 (0.96-2.30) for adult leukemia in the highest exposure category. This is is less likely to be due to bias than RR = 1.2 from the meta-analysis.	
(A7) Canadian studies of childhood leukemia are heterogeneous from other studies (possible indication of bias effect).	(F7) The studies in the comparative analysis all use state-of-the-art methods for occupational cancer cohort studies. The cohort method greatly reduces selection and information bias. The significant association from these high-quality studies is not likely to be due to bias, making	

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
	them evidence for causality.	
(A8) The low response rates of the measurement studies increases the possibility of non-response bias.	(F8) As shown by both meta-analyses from Greenland and Ahlbom, the McBride study is homogenous with the other studies; the reason why the Green study is different from all other studies may be due to bias.	
(A9) Hatch et al. (Hatch et al., 2000) show that the results of the Linet (Linet et al., 1997) study could in part be due to selection/non-participation bias.	(F9) Non participation bias: - Savitz (Savitz et al., 1988) estimated that if participation in his study had been greater, the risk estimate would have been increased. - No argument in favor of consistent upward bias (SES is usually associated with participation rate, but according to California data is only weakly correlated to personnally measured exposure (Lee et al., 2002). Plausible argument for downward bias due to non-response of controls away from power lines, who are less interested in EMF debate. - Because of their design, Scandinavian studies are not subject to selection or non-participation bias, yet their result is consistent with that of the US studies. Selection bias: - Preston-Martin's (Preston-Martin et al., 1996b) L.A. child brain cancer study is negative, therefore its case series can be used as a control series for another L.A. study. When used as such with London's (1996) case series, one sees an association similar to that obtained with the original controls. This suggests that London's control series is not subject to selection bias.	(C4) Even if one or more or all of the positive associations were due to bias, it would not change the results of the sign test, which shows that such a skewed pattern of positive results is extremely unlikely to be due to random effects.
(A10) Hatch (Hatch et al., 2000) demonstrated selection bias with regard to the association between front door measurement and ALL. This casts doubt	(F10) The association between front door measurements greater than 3mG and ALL fell from 1.9 (1.1-3.27) to 1.6 (0.98-2.61) when partial participants were included. This difference is not big and not statistically	(C5) Hatch (Hatch et al., 2000) provides some evidence of selection bias but does not conclude that it totally explains the findings in case-control studies. Her findings do not

BIAS		
AGAINST CAUSALITY	FOR CAUSALITY	COMMENT AND SUMMARY
on all case control studies of childhood leukemia.	significant.	apply to the Scandinavian studies

TABLE 8.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Since most causes of leukemia are unknown, it is impossible to rule out confounding, particularly when associations are not very large.	(F1) All known, suspected, and even speculated confounders were controlled for in most study since W&L.	(C1) The existence of a strong, yet unidentified and not even hypothesized confounder present in every population studied is less plausible than accepting EMF as the causal factor.
(A2) Traffic density has been found to be associated with both wire coding and childhood leukemia.	(F2) Savitz (Savitz et al., 1988) found that the association with traffic was not strong enough to explain association with wire coding. Long, in-depth research project aimed to prove traffic fumes as the causal agent concluded that traffic was probably an effect modifier (Pearson et al., 2000). Controlling for traffic density had no effect in the meta-analyses.	(C2) Confounders, like biases, may act both to increase or decrease an association. It is not plausible to believe that in all the diverse populations studied (both occupational and residential, children and adults, different continents, different methods of exposure assessment) all unspecified confounders acted consistently to create an artifactual association.
(A3) Mobility has been associated with wire codes and with leukemia.	(F3) Hatch et al. (2000) determined that known confounders were an unlikely explanation of the leukemia association in their study and that mobility was not associated with leukemia risk and was thus not a confounder.	
	(F4) An unknown, unspecified confounder must be strong risk, fast acting (e.g., probably not an initiator), and/or strongly correlated to MF surrogates. Yet it has escaped detection so far. There are no plausible candidates meeting this requirements.	
	(F5) There are convincing quantitative argument against the plausibility of confounding by an unknown factor (Langholz, 2001).	
	(F6) Most studies reporting an association do not rely on wire coding. Moreover, not all wire code studies show an association with mobility (Preston-Martin et al., 1996).	

TABLE 8.2.4

STRENGTH OF ASSOCIATION (HOW EASILY CAN THIS ASSOCIATION BE INFLUENCED BY FACTORS OTHER THAN CAUSALITY?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Association is not strong, which make the reviewers less confident that it is not due to artifacts.	(F1) An observed RR of 1.3-1.5 is probably equivalent to a true RR of about 2 because of random misclassification of exposure in residential environments.	(C1) Some agents at high ambient or occupational doses have effects that are truly close to the resolution power of epidemiology. In an individual study an effect of that size is viewed with suspicion. When it recurs in many studies without a plausible candidate confounder, the lack of an association easily distinguishable from epidemiological limitations does not lower the confidence of these reviewers much if at all.
	(F2) The inevitably poor exposure assessment in occupational studies probably results in even stronger bias toward the null.	
	(F3) Most hazardous agents at ambient doses do not produce strong risks.	
	(F4) The hypothesis under consideration argues that EMF is one of many risk factors for leukemia, not the only and not even the main cause. herefore a small increase in risk is all that can be expected.	

TABLE 8.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the studies failed to show a statistically significant risk. If there is any consistency, the pattern shows consistently inconclusive results.	(F1) In the absence of an effect, one would expect studies to yield relative risk estimates greater or smaller than one with equal frequency. Instead, when we inspect Figure 8.1.1 summarizing the adult leukemia studies reviewed by Kheifets (1997) or Figure 8.2.1, representing the 44 studies in Table 8.1.3, one finds that the vast majority of relative risks are above 1. When examining the childhood leukemia studies in Table 8.2.5A and Figure 8.2.2, one finds that out of 18 studies conducted in different locales, with different study designs by different investigators using different possibilities of bias and confounding, 14 yielded a risk estimate greater than 1, and 2 additional studies had infinite relative risks because no controls had "high" exposures. Thus, the meta-analytic and pooled estimates of effect do not arise from a few large studies. Rather they reflect a general pattern. One must look for a causal explanation or consistent bias or consistent confounding. (Note: The Myers [1990] data was not available to Greenland and is not included in Table 8.2.5 or Figure 8.2.2.)	(C1) Lack of statistical significance is not related to the likelihood of causality, but to the study power.
(A2) The Tomenius(Tomenius, 1986) study reports a protective effect for childhood leukemia, not the positive association displayed in Table 8.1.5.	(F2) As explained above, the DHS reviewers adopted the same cutpoints used in the pooled analysis (Greenland et al., 2000). In that peer-reviewed and published paper, based on the original raw data of Tomenius (1986), the comparison between subjects exposed to fields > 3 mG vs. those exposed to less than 1 mG shows a risk for the high-exposure subjects.	(C2) If EMF is a promoter, co-promoter, or growth modifier, the endpoint also depends on the presence in the environment of an initiator and possibly a promoter. Hence, complete consistency between studies cannot always be expected.
		(C3) The pattern of results is undeniably skewed toward a positive association. Given the very small probability of this happening by chance, the pattern increases the confidence in a causal effect.

Figure 8.2.1 Pattern of Relative Risks of Adult Leukemia from Table 8.1.3 Including Electric Railroad Engineers

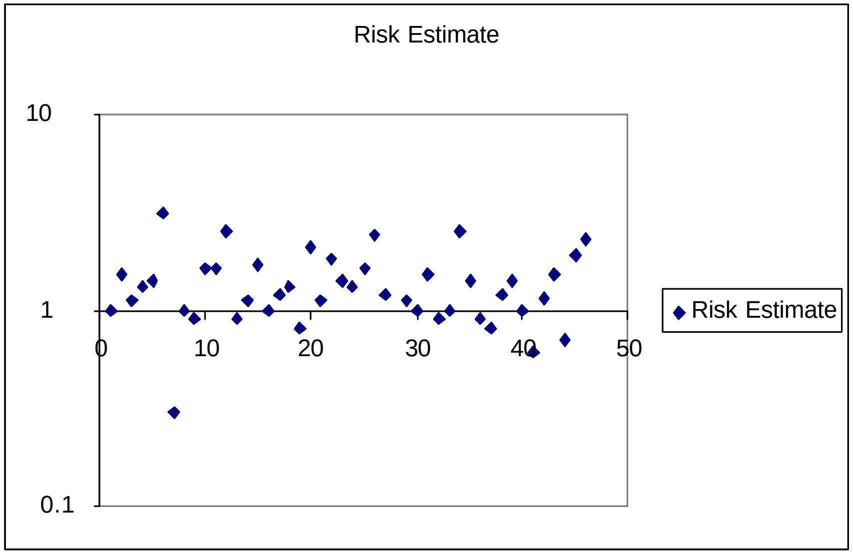
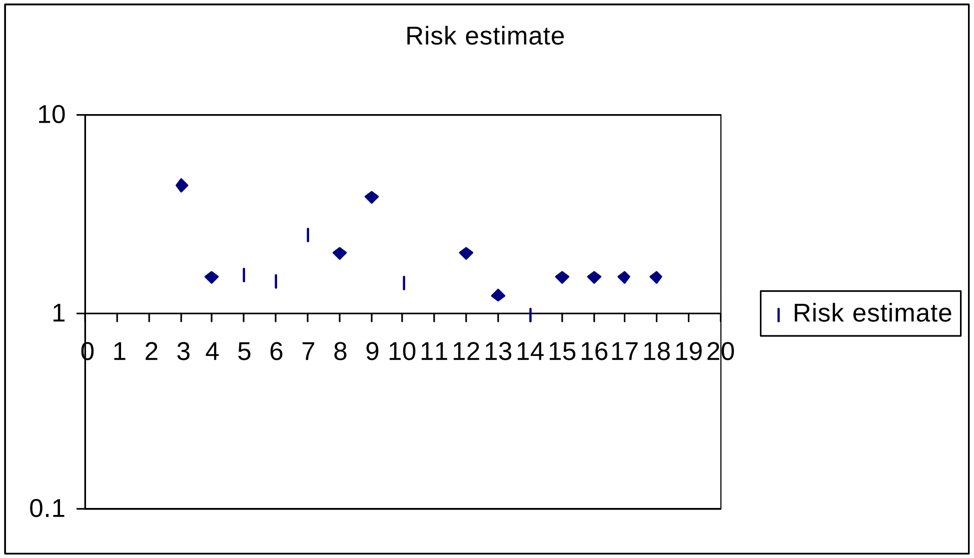


TABLE 8.2.5A SUMMARY OF THE CHILDHOOD LEUKEMIA STUDIES (COMPARING EXPOSURE > 3 MG VS EXPOSURE < 1 MG)

STUDY #	AUTHOR	COUNTRY	RISK ESTIMATE	BINARY OUTCOME FOR >0.3 µT
1	Coghill	UK	no controls	?
2	Dockerty	New Zealand	no controls	?
3	Feychting	Sweden	4.44	+
4	Linet	USA	1.51	+
5	London	USA	1.53	+
6	McBride	Canada	1.42	+
7	Michaelis	Germany	2.48	+
8	Olsen	Denmark	2.00	+
9	Savitz	USA	3.87	+
10	Tomenius	Sweden	1.41	+
11	Tynes	Norway	no cases	?
12	Verkasalo	Finland	2.00	+
13	Green	Canada	1.23	+
14	UK	UK	0.97	–
NON-MEASUREMENT STUDIES			**RISK FOR THE HIGH EXPOSURE GROUP**	
15	Wertheimer	USA	2.28	+
16	Fajardo	Mexico	1.64	+
17	Coleman	UK	1.70	+
18	Petridou	Greece	1.39	+

FIGURE 8.2.2 BASED ON TABLE 8.2.5A



Note: the last four studies, based only on wire code classification, have all reported a risk estimate > 1.0 However, the numerical value of the risk estimate is not comparable to that of studies using a quantitative exposure assessment. In this graph they have been assigned an arbitrary value of 1.5, simply to indicate that the point estimate is > 1.

TABLE 8.2.6

HOMOGENEITY (ARE THE POSITIVE STUDIES CONSISTENT WITH EACH OTHER OR ARE THER LARGE DIFFERENCES BETWEEN THEIR FINDINGS?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Of the wire code studies, one (Linet, 1998) shows no risk whatsoever, one (Fulton et al., 1980) is so flawed that the leading author, after publishing a negative result, used the same data to co-author a second paper with positive findings.	(F1) The pooled analysis by Greenland et al. (Greenland et al., 2000) concluded that all studies relying on calculations or measurements of exposure were homogeneous. Similarly, Kheifets (Kheifets, 1997) found that adult occupational studies (composing most of the data base) were not heterogeneous.	(C1) Most of the studies are consistent with the pooled analyses risk estimates.
(A2) The other wire code studies, showing no threshold of risk, are homogenous between themselves and with the Green study, but not with the results of the studies using a continuous exposure assessment metric.	(F2) Wiring practices differ from one locale to another. The original Denver wire code is unlikely to be a reliable universal exposure assessment protocol.	(C2) Some discrepancy may be expected due to methodological limitation.

TABLE 8.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all childhood studies show a clear dose response. While the recent pooled analysis and the Linet and the UK studies show evidence of a threshold, no such threshold was suggested by earlier studies.	(F1) All studies use surrogate exposure measures. The true exposure metric or optimum dosing schedule is not identified, therefore the surrogate-response curve is only loosely related to the true dose-response curve. Nevertheless, children studies suggest increasing risk with increasing exposure. The question of threshold depends on which surrogate is used and may reflect the fact that different surrogates measure different EMF properties. Spot measurements measure the mode of the exposure distribution (e.g., the most common value), while wire codes are more related to the maximum capacity of the electrical installations.	(C1) There is no biological or logical reason to believe that the dose response should be linear with no threshold or ceiling. The suggestion that certain biological processes may only be perturbed up to a point and no more is perfectly plausible. Greenland's (Greenland et al., 2000) systematic presentation of data shows no evidence of a historical shift in what the dose-response data.
(A2) Adult leukemia studies of electric train operators, in which the exposed group is often exposed to fields (100mG) many times higher than the that of the reference group (1mG), and even electrical workers (10 mG), show no evidence of a proportionally high risk.	(F2) The adult studies are consistent with a sigmoid risk function. -Clearer associations found with highest exposure group. -Evidence of stronger risk if exposed at work AND home (Feychting et al., 1997). -Some evidence of stronger risk with longer duration of employment (Savitz, Checkoway & Loomis, 1998a). -Theoretical data show that misclassification of exposure may increase risk estimate in intermediate exposure category (Dosemeci, Wacholder & Lubin, 1990), (DelPizzo, 1992). -Saturation of effect is consistent with proposed mechansims (e.g., disrupted hormone production, depression of immune system, ODC production).	(C2) The fact that extremely high exposures do not convey a proportionally higher risk deserves further investigation, but does not cancel the fact that, overall, there is evidence that within the range of common residential exposure more is worse, adding to the confidence of causality.

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A3) Symmetry arguments from physics suggest that any dose response should be by the square of the magnetic field intensity. It is not. Therefore, one's confidence in causality should fall sharply.	(F3) See biophysics arguments in Table 4.1.	(C3) The "square of field" argument is overly simplistic and unconvincing.
		(C4) Most studies could not investigate this issue appropriately because of limits in their size.

TABLE 8.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The hypothesis is not consistent with empirical observations. There is no evidence of an increase in leukemia rates with increase of power consumption.	(F1) If high end (3 mG) exposure produced risk, then even a doubling of the population exposure will not necessarily produce an increase in leukemia rate observable above normal historical fluctuations.	(C1) Ecological studies are insensitive and non-specific. An estimated attributable risk of 3-4% can be hardly demonstrated by incidence data.
(A2) The Swedish study is either internally inconsistent (if all subjects are included), or inconsistent with other studies (if limited to single-family homes).	(F2) Swedish study results limited to single-family homes are not inconsistent with pooled analysis.	(C2) The different sensitivity of field calculation when applied to single-family homes and apartments is a convincing explanation for the internal inconsistency of the Swedish results.
(A3) The Green (Green et al., 1999b) study shows a dose-response pattern different from that of the other studies.	(F3) Exposure estimates by calculation could not reliably predict the field in apartment homes and single family homes. (Feychting & Ahlbom, 1993). Therefore, the resulting misclassification bias may well account for the internal inconsistency between risk in single family and apartment homes.	(C3) On the face of it, the Green (Green et al., 1999b) study is puzzling, but its sample is too small to rule out a dose response similar to that suggested by the pooled analyses.
(A4) Jaffa (Jaffa, Kim & Aldrich, 2000) has shown that the Feychting study (Feychting & Ahlbom, 1993) relied on historical current flow data whose accuracy was too crude to have been able to make an accurate historical reconstruction of fields within the homes. The better prediction of risk by these estimates than concurrent measurements suggests that something is wrong with this study and by	(F4) Jaffa (Jaffa et al., 2000) is invoking non-differential exposure misclassification to explain away four well-conducted cohort studies. On average, non-differential misclassification should not be producing false-positive associations.	(C4) The reviewers acknowledge that the data available for reconstructing historical exposure was subject to non-differential misclassification but doubt that this produced false-positive results in this and the other Scandinavian studies.

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
extension, all the Scandinavian studies. They should all be ignored.		
(A5) The Milham (Milham & Ossiander, 2001) observation that death registrations from toddler childhood leukemia increased between 1920 and 1950 in just those states that had widespread electricification is not due to electrificiation. The opinion of Court Brown and Doll (Court Brown & Doll, 1961) notwithstanding, the apparent increase in leukemia death registrations could indeed be an artifact of diagnosis. The diagnosis and understanding of leukemia in the early part of the 20th century was quite different from today. The 1908 edition Diseases of Children by Pfaundler and Schlossman (Pfaundler & Schlossmann, 1908) speculates on an infectious origin, describes the blood as milky in color, and the course often brief. The importance of microscopic blood examination is already recognized. In the 1930s (Pfaundler & Schlossmann, 1935), the same textbook points out that the color of the blood depends on the degree of leukocytosis (that is, less obvious cases were now being recognized). The time from diagnosis to death of this febrile illness is described as being 1-3 months. It seems quite possible that the increased access to electricity was correlated with the increased access to physicians who in turn had access to microscopic blood tests during the brief course of this terrible childhood illness.	(F5) Court Brown and Doll (Court Brown & Doll, 1961) are not alone in taking this increase in death registration in England and the United States seriously. Cooke (Cooke, 1942),Gilliam (Gilliam & Walter, 1958), and Fraumeni (Fraumeni & Miller, 1967) hoped to find some explanation for it. There were many rural areas where government sponsored electrification may not have been well correlated with access to medical care.	(C5) Despite the interest in this pattern, which was first noticed 40 to 60 years ago, the possibiltiy of trends in diagnosis and death registration have to be taken seriously.
(A6) If as Milham avers (Milham & Ossiander, 2001), the threefold increase of toddler leukemia deaths in electrified areas is CAUSED by exposure to magnetic fields, the reviewers have a problem in reconciling this population increase with the results of the well-conducted epidemiology studies. The reviewers know from the studies in Table 8.1.4 that only a small proportion of the children in an	(F6) No one is completely free of magnetic field exposure, so the recent studies are analogous to comparing 2-pack-a-day smokers to 1-pack-a-day smokers instead of non-smokers. It is quite possible that there are effects at lower levels of magnetic fields that exposure misclassification has obscured. The increased risk was occurring to some degree at all non- zero levels of magnetic field and was not	(C6) It IS possible to distinguish 2-pack-a-day smokers from 1-pack-a-day smokers epidemiologically. The vast majority of leukemic and healthy children have exposures below 2 mG and there is plenty of data to see if there is evidence of risks conveyed by low exposures as compared to very low exposures. Greenland's analysis reproduced in Table 8.1.5 does not provide much support for that. Hence,

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
electrified community accumulate a 2-4 mG exposure. For the apparent rate in the entire community to seem to triple, the rate in this small exposed group would need to increase several hundredfold. Even with random misclassification, it seems highly implausible that the recent studies should be missing such an effect.	restricted to the small group with the highest exposure.	Milham's (Milham & Ossiander, 2001) observation has not increased the reviewers' degree of certainty much if at all.

TABLE 8.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See “General Issues” chapter.		

TABLE 8.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See “General Issues” chapter.		

TABLE 8.2.13

SPECIFICTY AND OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See “General Issues” chapter.		

TABLE 8.2.14

SUMMARY TABLE FOR DISEASE			
	HOW LIKELY IS THIS PATTERN OF EVIDENCE UNDER:		
	THE "NO EFFECT" HYPOTHESIS	THE HYPOTHESIS OF CAUSALITY	EFFECT ON CERTAINTY
Chance is not a likely explanation.	Very unlikely	Very likely	Increases certainty
Bias not proven.	Possible	Possible	Pulls down certainty only slightly, if at all
Confounding not identified.	Possible	Possible	No impact
Combined chance, bias, confounding.	Possible	Possible	Pulls down certainty only slightly, if at all
Strength of association.	Possible	Possible	No impact
Consistency: most studies show increase in risk.	Unlikely	Very likely	Increases certainty quite a lot
Homogeneity: meta-analytical results or other summary risk estimates are not driven by a few studies with large risk estimates, but most studies paint a similar picture.	Possible	Likely	Increases certainty a bit
Dose response.	Unlikely	Likely	Increases certainty somewhat
Coherence/visibility.	Possible	Possible	No impact
Experimental evidence.	Possible	Possible or likely	No impact or slight decrease in certainty
Plausibility.	Possible	Possible	No impact or increases certainty somewhat
Analogy.	Possible	Possible	No impact
Temporality.	Possible	Possible	No impact
Specificity and association with other diseases.	Possible	Possible	No impact

8.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

8.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

Reviewer 1 (DelPizzo)

Childhood Leukemia

Many of the attributes of the epidemiological evidence considered in this evaluation share similar characteristics, irrespective of the endpoints to which they refer. Therefore, some of the considerations described below apply to other endpoints also, and this reviewer will refer to them repeatedly when other endpoints are evaluated.

Bias: Reviewer 1 sees no evidence of a clear bias common to all or most studies that can explain away the association. While this reviewer believes that all studies are affected by some small degree of bias, the net effect of these unidentified biases should be null. Even considering a worst-case scenario, in which the results of all studies using random digit dialing to recruit subjects could be ***totally*** explained by bias, the p-value of the sign test would not increase to the point where the reviewer's judgment would be affected.

Confounding: See bias.

Strength of association: It was never suggested, even by the hypothesis generating studies by Wertheimer and Leeper, that exposure to EMF was a strong risk factor for childhood leukemia or any other endpoint. If it were, it would have manifested itself in clearly visible clusters and historical trends. There is no reason to believe that the association needs to be strong to be credible. An intrinsically weak association is much more consistent with the fact that these fields are non-ionizing and transfer a minimal amount of energy to the living organism. This attribute does not affect Reviewer 1's degree of certainty in the causal nature of the association.

Consistency: This is the strongest factor arguing for causality. Not one of the studies reviewed is inconsistent with a weak positive association, while many are inconsistent with a null effect. Considering that these studies were conducted over a period of almost a quarter of a century, in different nations in four different continents, using different study designs and analysis methodologies, the possibility that these results are due to a common bias or confounder which has escaped identification, or to a host of diverse biases or confounders which, by chance, almost always biased the risk estimate upward and never downward (which should be equally probable) is virtually ruled out.

Homogeneity: According to Greenland et al. (Greenland et al., 2000), studies using measurements or calculations to estimate exposure are homogenous (consistent with each other), while those using wire coding or proximity to power lines are not. The former conclusion increases this reviewers degree of certainty considerably because these studies were often different in design and execution. The latter does not decrease it because the effectiveness of wire codes are very much dependent on local wiring practice, therefore heterogeneity of results is to be expected.

Experimental Evidence

There is clearly no supportive experimental evidence that exposure to EMF increases the leukemia risk in laboratory animals. However, the literature is full of experimental results that contradict theoretical predictions that environmental EMFs are incapable of inducing biological effects. The theorists response to these results is far from convincing. In some cases they have speculated that these are artifactual results due to microchanges in temperature, in some cases they have been dismissed without explanation. It is Reviewer 1's opinion that the strongest argument for a low prior confidence level is one of dose, that is, that environmental EMFs levels are too low to have observable effects. Thus, the credibility of these experimental results are crucial, even if they do not directly pertain to the endpoint under evaluation. The question for Reviewer 1 is: are false-positive results in absence of a true causal effect more or less likely than false negatives in the presence of a true effect? False positives are possible, but false negatives are more then possible. Considering the absence of a clear theoretical model to guide the experimentalist in designing and conducting the experiment, the intrinsic experimental difficulties of studying a complex system (whether *in vivo* or *in vitro*), the complex nature of the EMF mixture of components and attributes and the engineering challenges in designing exposure systems and measuring the many parameters involved, false negatives are a virtual certainty.

Other associations: Since this is the first association to be evaluated, its credibility should not be influenced by other associations that have not been evaluated yet.

Dose response: Several studies detected a statistically significant dose-response trend. The Greenland (Greenland et al., 2000) pooled analysis shows clearly that higher fields correspond to stronger associations.

Visibility: No additional comment to those presented in the discussion.

Plausibility: No additional comment to those presented in the discussion.

Analogy: No additional comment to those presented in the discussion.

Temporality: The Swedish study is the only one where this attribute can be explored. The fact that the association exists with exposure calculated using historical current load data, but not with that calculated using contemporary loads argues in favor of causality.

Conclusion for Childhood Leukemia

None of the evidence speaks convincingly against the hypothesis of no risk, while the consistency of the association speaks strongly in favor of the hypothesis of causality and some of the controversial evidence is harder to explain under the hypothesis of no risk than under that of causality. This reviewer's opinion is that the consistency of the pattern of results by itself is sufficient to increase his level of confidence above 50%. The presence of some experimental results unexplained under conventional biophysical mechanisms, some evidence of dose response, and the homogeneity of the studies, all compound to add credibility to the risk hypothesis. Therefore, Reviewer 1's posterior level of certainty in a causal association is high, around 95, or in the category, "strongly believe" that EMFs increase the risk of childhood leukemia to some degree. On a certainty scale from 0 to 100 his confidence bounds range from 70 to 100.

Conclusion for Adult Leukemia

Most of the arguments for causality in the evaluation of childhood leukemia apply to adult leukemia as well. The pattern of results is slightly less consistent, the dose-response relationship much less clear, but having determined that EMFs are virtually certain to be a risk factor for childhood leukemia, the confidence in the causality of the adult leukemia association is also boosted. This reviewer's posterior level of confidence is about 85 with a range from 60-95. Thus, he is "prone to believe" that EMFs increase the risk of adult leukemia to some degree.

IARC Classification: In the EMF case, the animal and mechanistic evidence is less consistent and of lower quality than the human evidence. Therefore, since the IARC criteria rank animal and mechanistic evidence below human evidence, the Group 1 classification (the agent or mixture is carcinogenic to humans) can only be assigned if the human evidence can be regarded as "sufficient evidence of carcinogenicity." For this to happen, chance, bias, and confounding must be ruled out with reasonable evidence. The difficulty is to assign a precise meaning to the term "reasonable." Reviewer 1 believes the safest method is to use a comparative approach and question which of all the possible alternative explanations is more reasonable than the others.

This reviewer believes that for childhood leukemia this is the case, for the reasons given below:

Chance: By chance effect Reviewer 1 considers not only the sampling variations, but also the effects of biases and confounding that escape identification or even reasonable suspicion. For example, misclassification bias can be reasonably suspected in all EMF studies. Recall bias can be suspected in some occupational studies. Confounding from SES or subject mobility have been suspected, even if not confirmed. In all these cases, the direction of the point estimate bias can be anticipated, even if not confirmed or quantified. These are not "random biases or confounders." However, to suggest that since the etiology of childhood leukemia is unknown it is possible that unidentified confounders exist, cannot be controlled, but may affect the risk estimates, implies the possibility that this bias may be toward or away from the null. There is no reason to believe that biases in one direction are more likely than biases in the other direction. These are random events that are accounted for by an appropriate statistic test, such as determining the p-value using a sign test.

In the case of childhood leukemia, performing such a test on the results listed in the most recent meta-analysis (Wartenberg, 2001), combining the results of the few studies relying on proximity to exposure sources alone with those using measurements or calculations, yields a p-value of less than 0.001 for the hypothesis that residential EMF exposure conveys a risk greater than one. Therefore, Reviewer 1 concludes that chance is not a reasonable explanation for the observed positive association.

As for bias and confounding acting to create an artifactual association, all the obvious candidates and many very speculative ones have been considered. In some cases, these have managed to reduce the strength of the association, or at least to suggest a downward movement of the point estimate, but not to fully explain the positive association.

One possibility is that the positive associations reported over two decades of investigations, in several diverse locales, using a variety of study designs and of exposure assessment surrogates, are mostly due to a host of subtle biases or confounding agents that exist, some acting in one locale, some in another, some affecting one study design, some another, and all affecting the study results in the same direction. This is not a reasonable explanation.

The remaining question is whether it is reasonable to believe that one or two unsuspected biases and/or unidentified confounders exist that explain enough positive studies so that the remaining ones can be attributed to chance. What appears to be unreasonable here is the fact that such sources of error, which would have to be powerful and consistent, would remain unidentified over twenty years of efforts, notwithstanding the powerful social and economic motivations and resources to do so.

In summary, keeping in mind that accurate and consistent exposure assessment and ascertainment of the true dose response relationship is complicated by the fact that EMF is a mixture of agents, rather than a single factor, and this fact alone introduces inconsistencies between studies, it seems more reasonable to believe that the positive association reported by so many and diverse studies is indeed causal rather than due to such undefined and implausible alternative explanations.

While the lack of strong animal and mechanistic evidence is frustrating, in Reviewer 1's opinion the human evidence meets the criteria to justify a Group 1 classification.

Adult Leukemia

Most of the considerations of the childhood leukemia assessment apply here. Chance is even less likely as an explanation, given the larger number of studies (p = 0.000). However, since most of the studies are occupational, they are slightly more homogeneous than those of childhood leukemia, sharing a somewhat more similar environment and a slight possibility that recall bias may have played a greater part. Nevertheless, it still borders on unreasonable to believe that bias or confounding may be responsible for over 30 independent reports of positive associations and yet have eluded a positive identification.

Reviewer 1 cannot bring himself to accept chance, bias, or confounding as a more reasonable explanation for the association than causality. Therefore, his assessment is again for a Group 1 classification.

Reviewer 2 (Neutra)

Childhood Leukemia

Degree of Certainty: With regard to childhood leukemia, Reviewer 2 noted that the pattern of associations in the 19 studies reviewed was unlikely to occur by chance and that the pooled analysis by Greenland et al. (Greenland et al., 2000) and meta-analysis by Wartenberg (Wartenberg, 2001) also suggested chance as an unlikely explanation. The different study designs and locations of the studies made a common bias, other than non-differential measurement error, unlikely. It also seemed that the combination of chance, bias, and confounding in all these studies was less likely than a true effect not much above the resolution power of epidemiology. Early in the 1990s, when the early studies seemed to point more to proximity to power lines than to measured fields, there was suspicion that some other environmental factor such as traffic density or social factor associated with neighborhoods where power lines were above ground, might confound the association and explain it. Greenland et al. (Greenland et al., 2000) point out that when the newer studies are analyzed together the association between leukemia and measured or calculated fields is more consistent than is the wire code association. Magnetic fields come partly from easily observed power lines which may correlate with neighborhood characteristics and partly from less visible internal sources, such as stray ground currents and wiring net currents which are more random and probably less correlated with social factors. Specific studies of traffic density and neighborhood characteristics have not explained away the association. Langholz (Langholz, 2001) suggests that putative confounders need to be very strong risk factors indeed to explain away the childhood leukemia/magnetic field associations. Kavet and Zaffanella (Kavet et al., 2000) have suggested contact with ground currents as a possible explanation. In favor of this hypothesis are the calculations which suggest that the current entering the bone marrow would be larger than physiological background noise. Thus there is a plausible physical induction mechanism. But there is no hypothesis, much less experimental evidence, suggesting a biological mechanism leading to physiological or pathophysiological change. There are no animal pathology studies. There are no studies to document if such exposures are correlated with home magnetic fields or how common are such exposures, which involve grounded children touching plumbing long enough to be effective. Common sense suggests that such events would occur a few times a week to a few times a day. Reviewer 2 looks at this alternative hypothesis as unlikely but worthy of investigation because if true, simple inexpensive measures could be taken to avoid them. Another hypothetical confounder is the presence of charged pollutant particles around power lines (Fews, Henshaw & Wilding, 1999a). These relate to high electric fields, particularly near transmission lines. There is little or no evidence, experimental or epidemiological to support this hypothesis; but if true it would have implications for mitigation and should thus be pursued. In short, Reviewer 2 sees little or no evidence of credible confounders for the EMF/childhood leukemia association and the possiblity of as yet unknown confounders reduces his certainty only slightly.

The analyses presented by Greenland et al. (Greenland et al., 2000) and Wartenberg (Wartenberg, 2001) increase this reviewer's confidence substantially, and his confidence would not be pulled down much for bias and confounding even though the size of the association is not much above the resolution power of the studies and the dose-response relationships at the scanty top of the exposure distribution are not very consistent.

The the lack of a clear mechanistic explanation of the physical induction step or the chain of events leading to pathology provides little or no support, but does not pull confidence down much because these streams of evidence based on selected aspects of the "EMF mixture" are prone to false negatives about the mixture itself. Also, the biophysical arguments that recognized effects seen experimentally above 1,000 mG are not relevant to the epidemiology about associations with a few mG means that experiments must be done at ambient levels to be convincing. This is a requirement that many agents would not be able to meet. Reviewer 2 notes the suggestive results from the chicken embryo studies and the MCF-7 cell lines and thinks they warrant further work before they would increase his degree of certainty much.

Reviewer 2 is convinced that high intensity pure sinusoidal 60 Hz or 50 Hz magnetic fields do not produce enough of an effect to be observed reliably in conventionally sized studies with the species tested. Since the epidemiology that triggered the animal pathology studies to begin with did not suggest that the EMF mixture conveyed monotonically increasing risk at very high doses, the way that often happens with pure chemicals, he was on record before these studies began that they ran a high risk of providing null results. For this reason the largely null results have not lowered his degree of certainty much.

The types of associations seen in the studies, related as they are to the rare highest associations, could have been easily missed in national leukemia trends as electrification gradually extended through the world in the 20th century. Court Brown and Doll (Court Brown & Doll, 1961) noticed that toddler leukemia death registrations began to climb in the 1920s and Milham (Milham & Ossiander, 2001) has shown that this mortality pattern appeared geographically at the same time that these areas received electrification. The increased mortality is around threefold, but this is a much larger increase than would be predicted by the recent epidemiological studies. For reasons given under "Coherence/Visibility," Reviewer 2 is inclined to view the changes in reported mortality as an artifact of diagnosis and was not much influenced by this evidence.

Thus, despite the fact that ALL streams of evidence are not supportive, the pattern of evidence in the many epidemiology studies is strong enough that this reviewer has moved upward substantially from the prior degree of certainty.

Given the prior probabilities for different ranges of relative risks which this reviewer held, and considering the pattern of all streams of evidence, the degree of certainty that the observed epidemiological associations are substantially causal in nature (for purposes of the policy analysis) would be best expressed as "close to the dividing line between believing and not believing" that EMFs increase the risk of childhood leukemia to some degree. The degree of certainty on a scale from 0 to 100 would be 54 with a range of confidence from 25 to 80.

IARC Classification: The IARC classification usually requires larger associations and clearer dose-response relationships than seen here to consider the epidemiology definitive, and with the lack of supportive animal pathology studies or mechanistic explanations, this body of evidence would receive a "possibly carcinogenic 2B" IARC classification, "limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals"

Adult Leukemia

Degree of Certainty: Reviewer 2 considered that the pattern of associations among the 41 studies reviewed by Kheifetz et al. (Kheifets et al., 1997b) in her meta-analysis was quite unlikely to have occurred by chance and the meta-analysis itself did not suggest chance as a likely explanation.

Many of these studies were state of the art, of different designs, and in different locations and unlikely to share a single bias which would have inflated the apparent association. No plausible confounders have been advanced.

There is a wide range of exposures in different occupations, with the highest being in electric train operators, yet these studies do not demonstrate larger associations than studies of workers with more moderate exposures. This pulls down confidence somewhat, but could reflect low power or a dose response which truly does not increase monotonically over the full range of real world occupational exposures.

As indicated for childhood leukemia and in the pro and con discussion even without the support of animal pathology or mechanistic explanations, Reviewer 2's degree of certainty moved substantially upward from the prior position on the basis of the pattern of epidemiological evidence.

Considering all the evidence, and the prior starting point, the degree of certainty for purposes of the policy analysis would be best expressed as "close to the dividing line between believing and not believing" that EMFs increases risk of adult leukemia to some degree with a range of confidence from 15 to 70 and a best judgment of 52 on a certainty scale of 0 to 100.

IARC Classification: Since IARC usually requires larger associations and clearer dose response than is present in these studies to consider the epidemiology definitive, and since the animal pathology experiments and mechanistic explanations do not provide much support, adult leukemia could be viewed as on the border between have inadequate and "possible 2B carcinogen." Reviewer 2 judges the pattern of epidemiological evidence for adult leukemia regardless of type to warrant a "possible 2B" classification", "limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals"

Reviewer 3 (Lee)

Childhood Leukemia

Degree of Certainty: Of the Hills criteria to evaluate the human evidence, the consistency of the positive relative risks across studies is the strongest and hence increases Reviewer 3's posterior considerably. The posterior is also increased slightly by evidence of this positive effect even after adjustment for confounders by the careful assessment of bias, by evidence of a dose response even with surrogate exposure measures, and by evidence of an association of EMF with other disease. The posterior is slightly decreased due to inadequate biological and animal evidence. Hence, the posterior degree of certainty for purposes of the policy analysis could be expressed as "prone to believe" that EMFs increase the risk of childhood leukemia to some degree. On a certainty scale from 0-100, the best judgment certainty would be 65 with a confidence range from 25 to 80.

IARC Classification: The human evidence is sound and credible and based on the strong consistency of positive results across studies. The probability of chance contributing to the positive effect is low. Known cofounders have been considered and the positive effect remains. Bias has been evaluated and is not a likely explanation of the observed positive effects. An effect has been observed even though surrogate measures have been used. The evidence is sufficient for a Group 2A classification, "probably carcinogenic to humans," since the animal studies are weak. However, a clear biological model has not been adequately demonstrated.

Adult Leukemia

Degree of Certainty: The human evidence of the adult leukemia studies is not as strong or as consistent as the childhood studies. Nonetheless, the posterior is increased by a relative likelihood of a consistent weak effect across these occupational studies. Also, the posterior is slightly increased by evidence of an EMF association with other diseases, in particular childhood leukemia. The posterior is slightly decreased by the fact that most of the studies with positive effects are occupational studies and are vulnerable to confounding and bias, by the lack of a dose response, and by the lack of supporting animal evidence. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "close to the dividing line between believing and not believing" that EMFs increase the risk of adult leukemia to some degree category. On a certainty scale from 0 to 100, this reviewer would give a 40 with a confidence range from 15 to 70.

IARC Classification: The human evidence is weak but consistent where chance explaining the pattern of the weak positive associations is low. However, bias and confounding cannot be completely ruled out. Also, the animal evidence is inadequate. The evidence as a whole is sufficient for a Group 2B classification, "possibly carcinogenic to humans."

SUMMARY OF REVIEWERS' CONCLUSIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Childhood Leukemia				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Strongly believe	
	2	2B	Close to dividing line	
	3	2A	Prone to believe	
Adult Leukemia				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Prone to believe	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

8.4 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 8.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
See discussion in Chapter 3.	

TABLE 8.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No empirical evidence of plateau, however: (C2) Studies on subjects exposed to very strong fields do not show proportionally high risks. (C3) Many of the hypotheses suggested to explain the association (depression of the immune system, disruption of endocrine system, co-promotion) can only potentially explain a finite effect. (C4) Spline regression (Greenland et al., 2000) is compatible with many risk functions including no-threshold . In summary: - No conclusions can be drawn at this time on plateau. - Suggestive evidence of a 2-3 mG threshold.	(I1) Insufficient evidence to determine existence of plateau, but some suggestion that lowering extremely high fields to high fields may not convey any benefit. (I2) Reasonably reliable evidence that mitigation of TWA < 2 mG exposure may not be required.

Table 8.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	

Table 8.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	

Table 8.4.5

EMF COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Little is known about risk factors for these diseases, but the few known factors are not strong and do not account for most of the incidence.	

Table 8.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
AGAINST RELEVANCE	**IMPACT ON POLICY**
(C1) This association, if true, would generate theoretical lifetime risk greater than those regarded as *de minimis*.	(I1) Could be considered for regulation if real.

TABLE 8.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	

TABLE 8.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Exposure assessment can be improved by measuring more field parameters (e.g., maximum personal exposure, time coherence, contact currents, etc.).	(I1) Identifying contact currents or shocks as explaining the epidemiology would affect mitigation strategies.

TABLE 8.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Childhood Leukemia: Italy: Principal Investigator: Magnani, due in about 5 years, marginal statistical power Japan: Principal Investigator: Kabuto, 2,000 cases, unknown prevalence of exposure Germany: Principal Investigator: Michaelis, 200 cases and 200 controls California: a) Principal Investigator: Buffler, 580 cases b) Principal Investigator: Folliart, Study of EMFs and Case Fatality (C2) Adult Leukemia: Britain: Principal Investigator: Harrington, Occupational Mortality in Utility Industry	(I1) Unlikely for the foreseeable future.

TABLE 8.4.10

CAPABILITY OF CHANGING ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There is only one study in progress for adult leukemia. (C2) The database for childhood leukemia is too large to be substantially modified by the few studies in progress. (C3) Some better insight on the dose-response relationship is possible, but unlikely.	(I1) Not likely in foreseeable future.

TABLE 8.4.11

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Further epidemiological studies of these rare conditions are unlikely to resolve controversy. Epidemiological studies of other more common endpoints that can be studied prospectively could help guide mechanistic and animal pathology studies.	(I1) Not known

8.5 CONCLUSIONS ON SCIENTIFIC RELEVANT ISSUES

Dose-response Issues

At least for childhood leukemia, the evidence suggests that little or no risk is incurrent for exposure lower than 2-3 mG and there is not much evidence to suggest that lowering very high fields (like those experienced by electric train operators) to high fields (like the fields near transmission lines) would modify risk much.

Research Policy

Future epidemiological studies should explore the relationship between more common endpoints that can be studied prospectively and various aspects of the EMF mixture, other than TWA.